Association of autonomic symptoms with disease progression and survival in progressive supranuclear palsy

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ABSTRACT

Background: Development of autonomic failure is associated with more rapid disease course and shorter survival in patients with Parkinson's disease and multiple system atrophy. However, autonomic symptoms have not been specifically assessed as a prognostic factor in progressive supranuclear palsy (PSP). We evaluated whether development of autonomic symptoms is associated with disease progression and survival in PSP.

Methods: A retrospective review of clinical data from consecutive patients with autopsy-confirmed PSP from the Queen Square Brain Bank between January 2012 and November 2016 was performed. Time from disease onset to four autonomic symptoms (constipation, urinary symptoms, erectile dysfunction and orthostatic hypotension) were noted. Time from diagnosis to five disease milestones and survival were calculated to assess disease progression and their risk was estimated through a Cox proportional hazards model.

Results: A total of 103 PSP patients were included. Urinary symptoms and constipation were present in 81% and 71% of cases, respectively. Early development of constipation and urinary symptoms were associated with higher risk of reaching the first disease milestone (respectively, HR, 0.88; 95% CI, 0.83 – 0.92; p< 0.001; and HR, 0.80; 95% CI, 0.75 – 0.86; p< 0.001) and with a shorter survival in these patients (respectively, HR, 0.73; 95% CI, 0.64 – 0.84; p<0.001; and HR, 0.88; 95% CI, 0.80 – 0.96; p=0.004). On multivariate analysis, Richardson syndrome phenotype was the other variable independently associated with shorter survival.

Conclusions: Earlier urinary symptoms and constipation are associated with a more rapid disease progression and reduced survival in patients with PSP.

Keywords: Progressive supranuclear palsy; autonomic symptoms; urinary; constipation; survival

INTRODUCTION

Although autonomic dysfunction in Progressive Supranuclear Palsy (PSP) is not as severe as in Parkinson's disease (PD) and multiple system atrophy,[1] several symptoms with a potential autonomic basis have been reported.[1–8] Autonomic dysfunction has been associated with shorter survival in multiple system atrophy (MSA),[9–12], PD,[13] and possibly dementia with Lewy bodies,[14] but autonomic symptoms have not been systematically assessed as prognostic factors in PSP. In this study, we investigate the impact of development of symptoms associated with autonomic dysfunction on the clinical progression and survival in a large group of pathology-confirmed cases with PSP.

MATERIALS AND METHODS

Study design

Consecutive patients between January 1st, 2012 and November 7th, 2016 with a pathology-confirmed diagnosis of PSP were selected from the Queen Square Brain Bank for Neurological Disorders (QSBB) in London, United Kingdom. Patients with comorbidities known to affect the autonomic nervous system (e.g., diabetic neuropathies) or insufficient information documenting autonomic symptoms and disease progression were excluded. The brain donor program was approved by a London Multi-Centre Research Ethics Committee and written informed consent was obtained from all donors.

Clinical Assessment

All patients were diagnosed and regularly assessed throughout their illness by hospital specialists (neurologists or geriatricians) in the United Kingdom. A systematic review of the medical records was performed by a neurologist with expertise in movement disorders (M.C.B.O.).

In order to exclude potential influence of external factors (e.g., medication), autonomic symptoms were only documented when persisting for more than 6 months and

not attributed to a non-neurological cause, determined by clinical judgement. The following symptoms with a potential autonomic origin were noted: (1) urinary urgency, increased daytime frequency, and nocturia without hesitancy as defined by the International Continence Society;[15] (2) constipation (<3 defecations per week, having to strain to pass stools, or regular use of laxatives); (3) symptomatic or documented orthostatic hypotension (OH) defined by a greater than 20–mmHg decrease in systolic blood pressure or a greater than 10–mmHg decrease in diastolic blood pressure on standing; and (4) erectile dysfunction in males. If autonomic symptoms were not documented on medical records, they were considered as absent. These symptoms were selected because they are well documented in medical records, clinically relevant and easily assessed in clinical settings.

Five milestones were selected to define disease progression: (1) dementia (i.e. cognitive impairment severe enough to significantly affect tasks of daily living); (2) unintelligible speech or the offering of communication aids; (3) severe dysphagia or the offering of percutaneous endoscopic gastrostomy; (4) dependence on wheelchair, and (5) placement in residential or nursing homecare. These milestones have been selected because they represent the different domains of impairment of functioning in PSP, including motor progression, cognitive impairment, and global disability.[11] They are clinically relevant and well documented in the medical records.

PSP phenotype was assigned to each case, based on the predominant initial clinical presentation: (1) RS;[16] (2) PSP-parkinsonism (PSP-P);[16,17] (3) Pure akinesia with gait freezing (PAGF);[18] (4) cognitive phenotype including patients presenting with corticobasal syndrome (PSP-CBS);[19,20] frontal lobe cognitive or behavioural presentation (PSP-F),[21] and speech and language disorders (PSP-SL).[22,23] PSP-CBS, PSP-F and PSP-SL groups are relatively rare, and they were merged into a cognitive phenotype based on common neuropathological grounds (predominant cortical rather than brainstem involvement) in order to facilitate statistical analysis.

Time from disease onset to development of first and each milestone, each autonomic symptom, diagnosis and death were calculated.

Control groups

Twenty controls without symptoms of a neurodegenerative disorder during life and no evidence of neuropathological condition on autopsy were selected from QSBB matched by gender and as closely as possible by age at death. Demographic data and autonomic symptoms were noted using the same criteria described for PSP patients. Data on autonomic symptoms and clinical progression from a group of 100 patients with pathology-confirmed Parkinson's disease from the QSBB were used as a disease control group. Further details on participant selection and assessments can be found somewhere else.[13]

Neuropathological Assessment

Formalin-fixed brain tissue samples were examined using routine stains supplemented by immunohistochemical analysis in representative brain regions for amyloid beta (Aß) peptide, hyperphosphorylated tau-protein (AT8 antibody), TDP-43, ubiquitin, and α-synuclein according to Queen Square Brain Bank standard protocols. Established pathological diagnostic criteria for PSP were used.[24]

Statistical analysis

Clinical details were compared between PSP phenotypes, PSP versus Controls, and PSP versus Parkinson's disease groups. Chi-square or Fisher exact tests for categorical variables, and Mann-Whitney or Kruskall-Wallis (with Dunn test for multiple comparisons) for continuous variables were applied as appropriate.[25] Linear regression was performed to assess the association of time to each autonomic symptom with clinical features.

To visually assess the association of time from PSP onset to each autonomic symptom with the risk of developing a disease milestone or the risk of death (survival), patients were divided into 2 subgroups (e.g., early vs late) using the median value of each autonomic symptom, and Kaplan-Meier curves were plotted. Univariate Cox proportional hazards regression models were used to estimate the association between each autonomic

symptom with the risk of developing the first disease milestone and the risk of death. Multivariable Cox proportional hazards models were subsequently used and adjusted hazard ratios (HRs) and 95% CIs were estimated. Visual inspection of Kaplan-Meier curves and plots of scaled Schoenfeld residuals against time were used to assess the proportional hazards assumption. Censoring was considered to be uninformative.

Statistical significance was set at $P < 0.05$. Statistical analyses were performed using the STATA statistical software, version 14 (StataCorp).

RESULTS

Demographics and clinical characteristics

One hundred and seven PSP patients were identified within the study period. One patient was excluded because of insufficient clinical information and three because of concomitant type 2 diabetes mellitus. Main demographics and clinical data of the 103 PSP cases finally included in this study are shown in table 1. At least one milestone was reached by 102 patients (99%); with median [IQR] time from disease onset of 4.2 [2.8–5.7] years. Frequency and time to development of each autonomic symptom are described in Table 1 with data on comparison between phenotype groups. Phenotype groups did not differ in frequency of autonomic symptoms.

The association of autonomic symptoms to other clinical features is shown in Supplementary Table 1. Later development of constipation was associated with PAGF group (vs. RS, p<.001, linear regression). Earlier urinary symptoms and erectile dysfunction were associated with RS phenotype (vs. PSP-P, p<.001 and p=.04, respectively, linear regression) and with older age at onset (p<.001 and p=.005, respectively, linear regression).

Table 1: Comparison of clinical features and number of patients and time (years) to reach disease milestones and autonomic symptoms between PSP phenotype groups

	RS (n=53)	PSP-P (n= 23)	PAGF (n=5)	Cognitive (n= 22)	Total (n=103)	p Value
Number of females (%)	22 (42%)	5 (22%)	4 (80%)	8 (36%)	39 (38%)	NS*
Age at onset	66.8 [63.9–72.8]	66.3 [56.6–72.8]	69.1 [61.9–74.0]	65.9 [61.3–72.6]	66.8 [62.1–72.5]	NS
Age at death	74.3 [70.8–81.0]	76.5 [67.3–82.9]	82.7 [75.8–84.6]	74.7 [68.0–81.1]	74.6 [70.4–81.4]	NS
Disease duration	7.0 [5.5–8.4]	9.0 [7.0–13.2]	13.6 [8.3–16.3]	7.6 [5.6–9.6]	7.5 [5.7–10.0]	**p=.002[a]**, **p=.003[b]**, **p=.05[c]**, **p=.02[d]**
Time to diagnosis	2.3 [1.5–3.8]	5.2 [2.5–7.0]	3.0 [2.4–7.8]	3.3 [2.0–5.3]	3.1 [1.8–5.0]	**p<.001[a]**, **p=.03[e]**
Time to falls	n= 53 (100%)	n= 23 (100%)	n= 5 (100%)	n= 22 (100%)	n= 103 (100%)	-
	0.4 [0–1.8]	3.0 [1.0–5.0]	2.0 [0.2–5.7]	2.3 [0.5–4.0]	1.0 [0–3.3]	**p<.001[a]**, **p<.001[e]**
Time to first milestone	n= 53 (100%)	n= 22 (96%)	n=5 (100%)	n= 22 (100%)	n= 102 (99%)	NS*
	4.1 [2.6–5.0]	5.3 [3.5–9.1]	5.6 [5.3–12.5]	3.3 [2.3–5.1]	4.2 [2.8–5.7]	**p=.01[a]**, **p=.004[b]**, **p=.01[c]**, **p=.003[d]**,
Time to Wheelchair	n= 47 (89%)	n= 19 (83%)	n= 5 (100%)	n=21 (95%)	n= 92 (89%)	NS*
	4.7 [4.0–5.7]	7.0 [4.1–9.6]	6.1 [5.3–12.5]	5.0 [3.6–8.8]	5.0 [4.0–7.1]	**p=.02[a]**, **p=.01[b]**, **p=.04[d]**
Time to Dysarthria	n= 40 (75%)	n= 16 (70%)	n= 3 (60%)	n= 17 (81%)	n= 76 (74%)	NS*
	5.7 [4.0–6.6]	7.3 [5.7–12.2]	8.5 [5.5–15.0]	6.0 [4.3–7.4]	6.0 [4.3–7.4]	**p=.003[a]**, **p=.04[b]**, **p=.03[c]**
Time to Dysphagia	n= 38 (73%)	n= 16 (70%)	n= 2 (40%)	n= 14 (64%)	n=70 (69%)	NS*
	6.2 [4.7–7.6]	8.1 [5.8–11.8]	15.9 [15.1–16.8]	6.5 [4.9–8.4]	6.9 [5.1–8.6]	**p=.008[a]**, **p=.004[b]**, **p=.01[d]**
Time to Dementia	n= 18 (34%)	n= 13 (57%)	n= 2 (40%)	n= 16 (73%)	n= 49 (48%)	**p=.01***
	3.4 [1.8–4.4]	6.0 [3.5–11.3]	11.6 [9.2–13.9]	3.2 [2.2–5.1]	3.7 [2.3–6.8]	**p=.01[a]**, **p=.01[b]**, **p=.02[c]**, **p=.01[d]**
Time to Care	n= 46 (87%)	n= 20 (87%)	n= 3 (60%)	n= 20 (91%)	n= 89 (86%)	NS*
	5.0 [3.3–6.6]	6.8 [4.0–10.1]	13.7 [13.0–15.0]	5.6 [3.7–8.8]	5.6 [3.9–7.8]	**p=.04[a]**, **p=.001[b]**, **p=.005[d]**, **p=.01[f]**
Time to Constipation	n= 38 (72%)	n= 14 (61%)	n= 5 (100%)	n= 16 (73%)	n= 73 (71%)	NS*
	4.1 [2.9–6.2]	4.8 [3.6–6.1]	11.7 [6.9–12.5]	4.7 [2.7–6.8]	4.8 [3.4–6.7]	**p=.001[b]**, **p=.006[d]**, **p=.009[f]**
Time to Urinary symptoms	n= 43 (81%)	n= 18 (78%)	n= 3 (60%)	n= 19 (86%)	n= 83 (81%)	NS*
	2.7 [1.7–5.0]	5.4 [2.2–9.8]	4.0 [3.0–11.7]	4.3 [3.2–6.3]	4.0 [2.0–6.1]	**p=.006[a]**, **p=.03[e]**
Time to Erectile dysfunction (n= 64)	n=10 (32%)	n= 7 (39%)	n= 1 (100%)	n= 2 (14%)	n= 20 (31%)	NS*
	-2.0 [-7.4–0.8]	2.5 [0.6–5.8]	1.0	0.1 [-0.4–0.6]	0.4 [-3.0–2.6]	NS
Time to Orthostatic Hypotension	n= 2 (4%)	n= 5 (22%)	n= 0	n= 2 (9%)	n= 9 (9%)	NS*
	2.5 [2.0–3.1]	4.0 [0.5–5.7]	-	-0.1 [-2.0–1.8]	2.0 [0.5–4.0]	NS

Table 1 legend: Data are expressed as number (frequency) or median [interquartile range] NS= Non-significant. RS= Richardson syndrome; PSP-P= PSP-parkinsonism; PAGF= Pure Akinesia with Gait Freezing. Cognitive group is a composite of PSP-Speech/Language, PSP- Frontal/behavioural and PSP-Corticobasal Syndrome groups.
Kruskall-Wallis comparison between groups and Dunn multiple comparisons test: [a]RS vs. PSP-P; [b]RS vs. PAGF; [c]Cognitive vs. PSP-P; [d]Cognitive vs. PAGF; [e]RS vs. Cognitive; [f]PSP-P vs. PAGF. [*]Fisher exact test.

Comparison of autonomic symptoms with controls and Parkinson's disease patients

As some of the autonomic symptoms are common in older individuals, findings of PSP were compared with those of healthy controls. PSP patients had a higher frequency of all four autonomic symptoms (Supplementary Table 2) which could not be explained by additional neurodegenerative changes in the PSP group as both had similar concomitant neuropathological findings (Supplementary Table 3). When compared to Parkinson's disease (as a disease control with known autonomic dysfunction), PSP patients had less constipation and orthostatic hypotension, but did not differ in urinary symptoms and erectile dysfunction frequencies (Supplementary Table 2).

Association of autonomic symptoms with disease progression

Earlier development of constipation and urinary symptoms were associated with a significantly increased risk of reaching the first milestone (HR for constipation, 0.88; 95% CI, 0.83 – 0.92; p<.001; and HR for urinary symptoms, 0.80; 95% CI, 0.75 – 0.86; p<.001). Orthostatic hypotension did not affect the risk of reaching the first milestone; early erectile dysfunction increased the risk of reaching the first milestone, although this was not statistically significant (Table 2 and Figure 1).

Table 2: Cox Proportional Hazards Regression Models of Clinical Features for First Milestone and Survival

Autonomic symptoms	HR (95% CI)	p Value
First milestone		
Constipation	0.88 (0.83 – 0.92)	**<.001**
Urinary symptoms	0.80 (0.75 – 0.86)	**<.001**
Erectile dysfunction	0.92 (0.84 – 1.01)	.07
Orthostatic hypotension	0.86 (0.67 – 1.13)	.29
Survival		
Constipation	0.80 (0.75 – 0.86)	**<.001**
Urinary symptoms	0.86 (0.81 – 0.91)	**<.001**
Erectile dysfunction	0.93 (0.84 – 1.02)	.13
Orthostatic hypotension	1.00 (0.79 – 1.27)	.98

Table 2 legend: HR= Hazard ratio. The different forms of the main explanatory variables were considered in turn in different Cox proportional hazards regression models (not in the same model).

Association of autonomic symptoms with survival

Earlier development of constipation was associated with shorter survival (HR, 0.80; 95% CI 0.75 – 0.86; p<.001), as was earlier development of urinary symptoms (HR, 0.86; 95% CI 0.81 – 0.91; p<.001). Early erectile dysfunction or orthostatic hypotension did not significantly influence survival risk (Table 2 and Figure 2).

Other determinants of survival and multivariable analysis of survival predictors

Older age at onset, shorter time to falls and PSP phenotype, together with constipation and urinary symptoms, showed an association with survival and were used as explanatory variables in the multivariate Cox regression model (Table 3, Supplementary Figure1). Early constipation remained significantly associated with a 27% increase of risk of death per year after adjustment (HR, 0.73; 95% CI, 0.64 – 0.84; p<.001). Association between early urinary symptoms and shorter survival also remained significant, with a 12%

increase of risk of death per year (HR, 0.88; 95% CI, 0.80 – 0.96; p=.004). RS phenotype was the only other variable to maintain significance after multivariable analysis. (Table 3)

Table 3: Multivariable analysis of survival predictors

	Crude HR (95% CI)	p Value	Adjusted HR (95% CI)	p Value
Time to constipation (y)	0.85 (0.75 – 0.86)	**<.001**	0.73 (0.64 – 0.84)	**<.001**
Time to urinary symptoms (y)	0.86 (0.81 – 0.91)	**<.001**	0.88 (0.80 – 0.96)	**.004**
Male gender	1.23 (0.82 – 1.85)	.32	1.76 (0.93 – 3.31)	.08
Age at onset (y)	1.05 (1.02 – 1.07)	**<.001**	0.99 (0.95 – 1.04)	.74
Time to falls (y)	0.86 (0.78 – 0.95)	**.002**	0.94 (0.77 – 1.14)	.51
PSP phenotype				
PSP-P (vs. RS)	0.36 (0.21 – 0.63)	**<.001**	0.20 (0.07 – 0.57)	**.003**
PAGF (vs. RS)	0.23 (0.09 – 0.61)	**.003**	0.22 (0.03 – 1.55)	.13
Cognitive (vs. RS)	0.74 (0.45 – 1.23)	.25	0.93 (0.44 – 2.00)	.86

Table 3 legend: HR= Hazard ratio; RS= Richardson syndrome; PSP-P= PSP-parkinsonism; PAGF= Pure akinesia with gait freezing. Cognitive group is a composite of PSP-Speech/Language, PSP- Frontal/behavioural and PSP- Corticobasal Syndrome groups.

DISCUSSION

Although previous studies have shown association of urinary incontinence with shorter survival in PSP,[21,26] this is the first study to systematically assess autonomic symptoms as predictors of disease course and mortality in a large group of autopsy-confirmed PSP patients. Our findings showed that earlier development of constipation and urinary symptoms are significantly associated with more rapid disease progression and shorter survival. There is no association between the development of first milestone or death with orthostatic hypotension or erectile dysfunction, in contrast to MSA.[10]

One of the strengths of our study is that all patients had pathologically confirmed diagnosis, since it is conceivable that patients with parkinsonism and autonomic symptoms may be misdiagnosed with MSA and, therefore, clinical studies can underestimate the actual

prevalence and impact of autonomic symptoms in PSP. For example, six of our 103 patients (5.8%) had received a clinical diagnosis of MSA in life. Another study demonstrated a high prevalence of PSP cases with autonomic failure that were misdiagnosed in life as MSA.[27]

Prevalence of Autonomic symptoms: Autonomic symptoms tend to be more common in the elderly; for example, the prevalence of constipation lies around 33.5% in people aged 60-101.[28] Although not the primary aim of this study, the fact that all four autonomic symptoms were observed more frequently in PSP than in healthy controls suggests they could not be explained solely by autonomic dysfunction associated with age or additional concomitant neuropathologies in the PSP group. Except for OH, prevalence of all autonomic symptoms was similar to patients with Parkinson's disease. This is in keeping with other studies comparing both pathologies.[1–8] All together our findings suggest that there is an element of clinically relevant disturbance in most areas of autonomic function in PSP.

Autonomic symptoms and survival. The main finding of our study is that early development of constipation and urinary symptoms was associated with rapid development of disease milestones and shorter survival after adjustment for relevant variables. Classically, this more rapid course has been attributed in synucleinopathies to a more aggressive underlying neurodegenerative process although a recent clinicopathological study on Parkinson's disease failed to show any association between autonomic dysfunction and histological staging.[13]

Selective involvement of autonomic regulatory structures of the brainstem, spinal cord and hypothalamus has been proposed as the pathological substrate for autonomic dysfunction and poor prognosis in patients with MSA.[12,29] A previous neuropathological study of PSP demonstrated tau pathology in selected brainstem nuclei involved in autonomic control, with a role in regulating cardiovascular function and micturition networks. This is a possible explanation for some of these autonomic symptoms in PSP, although it failed to show any correlation with disease duration.[30] Another study described tau deposition in the Onuf's nucleus, the structure responsible for bladder and sphincter control, in PSP patients with urinary symptoms and abnormality of sphincter muscles on

electromyography.[31] In addition, because cortico-subcortical structures are responsible for voluntary control of micturition,[2] earlier urinary incontinence could reflect widespread involvement of the frontal lobe, although urinary symptoms were not associated with cognitive phenotypes in our study.

Autonomic dysfunction in PSP is not well understood, and although preganglionic involvement of central nervous system areas has been shown in neuropathological studies,[30,31] postganglionic involvement of nervous structures and other factors such as age, medications, immobility or dietary and water intake [32] could potentially influence the presence and severity of some of the autonomic symptoms assessed in our study. We would like to emphasise that in this study we assessed autonomic symptoms (rather than autonomic function) and that, although we tried to limit the influence of other non-neurological factors with strict inclusion criteria, we acknowledge that some of these symptoms may have a multifactorial origin. Our study was conducted using routinely collected clinical information on autonomic symptoms and we are unable to make any firm conclusions whether these symptoms are the result of dysautonomia due to direct involvement by the neurodegenerative process or secondary to the combination with other external factors. However, these results on PSP are in contrast with a similar study performed on PD, where every autonomic symptom was associated with a more rapid disease progression and reduced survival.[13]

We found that constipation and urinary symptoms, but not OH and erectile dysfunction, showed a significant prognostic value in our patients. In addition, different PSP phenotypes have not shown specific predilection for autonomic regulatory structures suggesting that the reported worse prognosis in PSP might not be due to global dysautonomia secondary to neuropathological involvement of autonomic structures and additional factors may influence this association. The selective influence of some of the autonomic symptoms on prognosis may be due to intrinsic morbidities and mortality associated with them (e.g. urinary symptoms may predispose patients to development of urinary infections).

Other predictors of survival. Several articles have described natural history and predictors of survival in PSP with conflicting results which may be partially explained by heterogeneity in the methodology. The most consistent predictors of survival appear to be RS phenotype,[11,33] early dysphagia,[21,26,34,35] early cognitive symptoms,[21,35] early falls,[21,26,36] and severity of disease measured by the PSP rating scale.[37,38] In our study, we found that older age at onset, shorter time to falls and RS and cognitive phenotypes were all associated with shorter survival, but only RS phenotype, in addition to development of constipation and urinary symptoms, remained significant after adjustment in multivariable analysis. It is possible that factors associated with RS phenotype are contributory to the shorter survival as this phenotype is associated with earlier falls.

The fact that RS and cognitive phenotypes are associated with shorter survival in comparison with PSP-P and PAGF (Supplementary Figure1) is in keeping with studies showing an inverse relationship between total tau burden and disease duration in PSP phenotypes.[39] For instance, PSP-P and PAGF phenotypes have less tau burden compared with PSP-RS and also have longer survival duration.[18,40] Additionally, despite a shift of tau burden from deep grey matter structures towards the cortical regions in PSP-CBS compared with PSP-RS, the overall tau burden and survival period are similar between these two phenotypes.[20]

Limitations. The retrospective nature of this study, with clinical assessments performed by different professionals with various levels of clinical expertise, without methodological homogeneity and the lack of confirmation with neurophysiologic cardiovascular autonomic testing are inherent limitations in clinicopathological studies using brain bank archival collection. This may have led to underreporting of autonomic symptoms, particularly in healthy controls, who may have not been as closely monitored as parkinsonian patients. Nevertheless, only patients regularly seen by hospital specialists throughout their disease (or general practitioners in the case of controls) with regular documentation were included in the study, and only autonomic symptoms with relevance to clinical practice were assessed to minimize documentation bias. Moreover, as health care is

free to access in the United Kingdom, controls included in the study had regular contact with primary care as part of public health and preventive medicine policies, which may have mitigated any potential surveillance bias. Despite the limitation of patients not having been assessed with neurophysiologic testing, the fact that the autonomic symptoms were clinically assessed means the results can be generalized to clinical practice where autonomic function tests are not always available. Although the merging of PSP-CBS, PSP-F and PSP-SL to facilitate statistical analysis into a cognitive group based on the predominant cortical involvement may limit the interpretation of the results of PSP subtype comparisons, it has no effect at all on the primary conclusions of the study. Brain bank studies tend to include more severe or atypical cases, which may account for some differences with clinical studies.

In conclusion, this study found that early onset of constipation and urinary symptoms is associated with more rapid disease progression and shorter survival. Constipation and urinary symptoms are common in PSP and increasing awareness and recognition in clinical settings will contribute to the improvement of patient counselling. These findings may also have important clinical implications as a more optimal management of autonomic dysfunction could potentially improve the prognosis on these patients. Further prospective studies assessing autonomic symptoms with pathological confirmation of the diagnosis are warranted to corroborate our findings.

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LEGENDS TO FIGURES

Figure 1: Kaplan-Meier curves of cumulative risk of first disease milestone amongst patients with PSP by time to development of each autonomic symptom (Early vs Late)

Figure 2: Kaplan-Meier curves of survival probability among patients with PSP by time to development of each autonomic symptom (Early vs Late)